



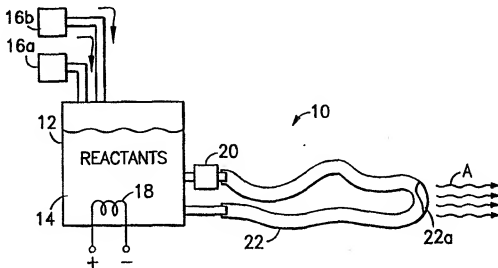
PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61B 5/00, 5/06</b>		<b>A1</b>	(11) International Publication Number: <b>WO 98/32370</b>
		(43) International Publication Date: 30 July 1998 (30.07.98)	
(21) International Application Number: PCT/US98/01200		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 20 January 1998 (20.01.98)		<p><b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	
(30) Priority Data: 60/036,246 24 January 1997 (24.01.97) US 08/929,782 15 September 1997 (15.09.97) US			
(71) Applicant: SPECTRA SCIENCE CORPORATION [US/US]; Suite 101, 155 South Main Street, Providence, RI 02903 (US).			
(72) Inventor: LAWANDY, Nabil, M.; 169 Eastwick Avenue, North Kingston, RI 02853 (US).			
(74) Agent: GREEN, Clarence, A.; Perman & Green, LLP, 425 Post Road, Fairfield, CT 06430 (US).			

(54) Title: CHEMILUMINESCENT SOURCES FOR PHOTODYNAMIC THERAPY AND PHOTOMEDICINE



(57) Abstract

An optical source (10) for exciting a photosensitive drug that responds to light within a predetermined band of wavelengths. The optical source uses a chemiluminescent source in combination with at least one fluoracer selected to output light within the predetermined band of wavelengths. The chemiluminescent source can be flowed during use. In one embodiment the chemiluminescent source is stored in a heated reservoir, and is pumped from the reservoir through a conduit, such as a catheter. A patch can be used for spreading the chemiluminescent source over a wider area. An active feedback system can also be used for controlling the output light. In preferred embodiments a plurality of reactants are mixed for forming a chemiluminescent source in combination with at least one fluoracer selected to output light within the predetermined band of wavelengths. The mixing of the reactants causes an excitation of the at least one selected fluoracer by energy transfer from an energetic intermediate in a chemiluminescent reaction to provide a fluorescent emission in the predetermined band of wavelengths.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

CHEMILUMINESCENT SOURCES FOR PHOTODYNAMIC THERAPY  
AND PHOTOMEDICINE

CLAIM OF PRIORITY FROM A COPENDING PROVISIONAL APPLICATION:

5 This patent application claims priority under 35 U.S.C. §1.119(e) from copending Provisional Patent Application No.: 60/036,246, filed January 24, 1997, entitled "Chemiluminescent Sources for Photodynamic Thereapy and Photomedicine" by Nabil M. Lawandy, the disclosure of which is incorporated by reference herein in its entirety.

10 FIELD OF THE INVENTION:

This invention relates generally to optically-based therapeutic procedures.

BACKGROUND OF THE INVENTION:

15 Photodynamic Therapy (PDT) uses specifically designed drugs such as Foscan® (Scotia Pharmaceuticals), ALA (DUSA) and Photofrin (QLT Phototherapeutics) to destroy rapidly dividing cells. These drugs are selectively retained or generated at rapidly dividing cells and are subsequently excited by light to produce the desired effects. The  
20 primary mode of activity usually involves energy transfer from these photoexcited drugs to  $O_2$  to produce superoxides or  $O_2$  in the singlet state. To date this excitation has been provided by lasers, lamps, and new materials such as LaserPaint™ (laser action in amplifying scattering media).  
25 Some of these sources are expensive and require complicated delivery systems.

OBJECTS OF THE INVENTION:

It is an object of this invention to provide an improved method and apparatus to excite an optically-responsive or photosensitive therapeutic drug.

- 5 It is a further object of this invention to provide an improved method and apparatus for generating light that can be used directly for photomedicine applications.

SUMMARY OF THE INVENTION

- 10 The foregoing and other problems are overcome and the object of the invention is realized by methods and apparatus in accordance with embodiments of this invention.

- 15 This invention teaches the use of static or flowing chemiluminescent materials to excite a photosensitive drug or to irradiate a tissue for performing photomedicine. Many reactions can be used for chemiluminescence, and include luciferase (Firefly reaction) and the oxalate ester/hydrogen peroxide ( $H_2O_2$ ) system. The latter reaction is commonly found in so-called "light sticks".

- 20 The fluorescers in the chemiluminescent reaction can be selected so as to emit exactly under the absorption band of many photosensitive drugs, such as those used in PDT, or those found in living systems, such as blood.

- 25 For example, rhodamine derivatives can be used for exciting the photoresponsive drugs Photofrin, ALA, PP IX, and Foscan®.

In order to sustain high luminous fluxes, the reaction can be created in a reservoir with a constant input of reactants and pumped through a catheter or a fluid

containing externally applied patch, depending on the procedure. Catheters are ideally suited for treating, by example, esophageal cancer, while patches are ideally suited for treating skin conditions, as well as head and neck cancers. The reactants can be heated to increase the reaction rates and produce higher optical power.

The use of patches for skin and oral cavity treatments can eliminate the need for anesthesia, and furthermore can allow the patient to continue the treatment outside of the clinical setting. Patches may be made to operate in a similar manner to light sticks, and can be initiated by a pressure rupture of a barrier, releasing the reactants into a transparent pouch. One side of the pouch may be reflective so as to enhance the delivery of light towards the target area.

Active feedback can be provided from the target area using, by example, a photodiode, so as to control the delivery of reactants to, and the output power of the reactants at, the target area.

In preferred embodiments of this invention a plurality of reactants are mixed for forming a chemiluminescent source in combination with at least one fluorester selected to output light within the predetermined band of wavelengths. The mixing of the reactants causes an excitation of the at least one selected fluorester by energy transfer from an energetic key immediate in the chemiluminescent reaction to provide a fluorescent emission in the predetermined band of wavelengths.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The above set forth and other features of the invention are made more apparent in the ensuing Detailed Description of

the Invention when read in conjunction with the attached Drawings, wherein:

Fig. 1 is block diagram of a system for delivering a flowing chemiluminescent source to a region of interest;

5 Fig. 2 illustrates a first embodiment of a patch suitable for being connected to the system of Fig. 1;

Fig. 3A illustrates a top view and Fig. 3B a cross-sectional side view of a second embodiment of a patch, wherein reactants can be mixed on demand for generating the  
10 chemiluminescent source;

Fig. 4 illustrates an embodiment of a catheter that is useful for esophageal and other applications; and

Fig. 5 is a block diagram of the system shown in Fig. 1, wherein active feedback is used.

15 DETAILED DESCRIPTION OF THE INVENTION

Referring to Fig. 1, there is illustrated a system 10 for flowing a chemiluminescent source. System 10 includes a reservoir 12 for containing a volume of reactants 14. Coupled to the reservoir 12 are a plurality of reactant  
20 sources 16a, 16b which provide, either continuously or on demand, measured amounts of reactants to the reservoir 12 so as to provide a desired intensity of emitted light. A heater 18 can be provided for heating the reactants 14 so as to increase the reaction rate, to produce a higher  
25 optical output, as well as to control the optical power. The reactants include at least one selected fluoescer, such as a rhodamine derivative, that is selected for its emission of a wavelength that optically excites a photosensitive drug of interest. The reactants also include

materials known for use in providing chemiluminescence, such as luciferase and the oxalate ester/hydrogen peroxide ( $H_2O_2$ ) system.

Suitable fluorescers for use with this invention include the following:

- 5 Coumarin 440
- Coumarin 480
- 9,10-diphenylanthracene (DPA)
- 10 Rhodamine 590
- Rhodamine 610
- Rhodamine 640
- Rhodamine tetrafluoroborate
- Sulforhodamine 640
- DCM
- 15 Kiton red 620
- Acridine orange

The enhancement capacity of  $TiO_2$  for different dyes (Ester, dye + Peroxide with and without  $TiO_2$  was confirmed for the following:

- 20 Rubrene (yellow emission)
- 9,10-bis(phenylethynyl)anthracene (yellow)
- Coumarin 480 (blue)
- 9,10-diphenylanthracene (DPA)

In the foregoing examples, the number following the compound name indicates the emission wavelength.

The teaching of this invention is believed to produce satisfactory results using peroxyoxalate chemiluminescent systems (PO CL). In these systems, oxalic acid derivatives react with hydrogen peroxide in the presence of a fluorophore to produce a bright emission characteristic of the fluorescer. This reaction proceeds via an energetic key intermediate, which is proposed to be 1, 2-dioxetanedione.

Other oxalate esters include the following.

- 35 Bis(2-nitrophenyl)
- Bis(4-nitrophenyl)
- Bis(4-nitro 3-trifluoromethyl)

Bis(4-nitro-2-formylphenyl)  
Bis(4-nitro-2,6-dichlorophenyl)  
Bis(2,4-dinitrophenyl)  
Bis(2,5-dinitrophenyl)  
5 Bis(2,4-dichlorophenyl)  
Bis(pentachlorophenyl)  
Bis(pentafluorophenyl)  
Bis(3-trifluoro-methylphenyl)  
Bis(3,5-di(trifluoro-methylphenyl)  
10 Bis(2,6-dimethylphenyl)  
Bis(4-methoxyphenyl)  
Diphenyl  
Phenylene  
Bis(2-naphthyl)  
15 Di-i-butyl  
Bis(2-cyano-2-propyl)  
Bis(2,2,2-trifluoro-ethyl)  
Bis(diphenylmethyl)

Another oxalate ester of interest is bis(2,4,6-  
20 trichlorophenyl) oxalate.

In an exemplary embodiment of this invention a Rhodamine derivative is excited by energy transfer from an energetic immediate in the chemiluminescent reaction, and provides a fluorescent emission in a desired band of wavelengths. A  
25 second emitter (e.g., a dye, chelate, or phosphor) can be used to coat a portion of structure, such as the catheter described below, to further shift the emission to a desired wavelength. A pump 20 is provided for pumping a flow of the reactants 14 through a conduit, such as a catheter 22, for  
30 delivering the chemiluminescent source to a region of tissue to be treated, as well as to control the output optical power. At least one portion of the catheter 22 is transparent to the light emission having the wavelengths used to excite a photosensitive drug of interest. Fig. 1  
35 illustrates the use of a single transparent region 22a for outputting light A having the desired wavelengths.

It can be appreciated that the reactants can be pumped into a waste tank (not shown), and need not be returned to the reservoir 12.



Fig. 2 shows an embodiment wherein a patch 24 is inserted into the catheter 22 such that the flow of reactants passes through the patch 24. The patch has at least one internal chamber or compartment capable of containing the flow of reactants as they pass through. The use of the patch 24 beneficially spreads the flowing chemiluminescent source over a wider area, which is useful for treating certain tissues such as skin. As in the catheter embodiment of Fig. 1, the patch 24 has at least one region 24a that is transparent to the light A having the wavelengths of interest.

Fig. 3A illustrates a top view and Fig. 3B a cross-sectional side view of an embodiment wherein a partially transparent patch 26 includes a plurality of reactant compartments or containers 26a, 26b which, when broken or ruptured by a mechanical deformation of the patch, enable the reactants to be mixed and thus provide the desired therapeutic light. Although two reactants are shown in Figs. 1 and 3A, it can be realized that as many reactants as are needed can be utilized in accordance with this invention. At least one of the reactants also contains the one or more selected fluorescers, or the fluorescer(s) could be provided in a separate compartment or container.

As is seen in Fig. 3B the patch 26 includes a transparent window portion 26c, and may include a reflector 26d, such as a layer of foil, disposed on an opposite surface for reflecting incident light towards the window portion 26c. The reflector 26d can be used as well in the embodiments of Figs. 1 and 2. A portion of the reflector 26d, or some other structure in the patch 26, could include the above-mentioned second emitter (e.g., a dye, chelate, or phosphor) in order to shift the emission to a desired wavelength.

Fig. 4 illustrates an embodiment of a transparent or partially transparent catheter 30 that is useful for esophageal and other applications. A flow of reactants is established through the catheter 30 for providing the  
5 desired light emission A. A set of heating coils or tape 32, such as a resistive heating strip, can be used to produce a desired non-uniform excitation profile to treat different regions with dose selectivity. The coils 32 are preferably of low wattage, and may be molded into or  
10 embedded within the catheter wall. The reflector 26d can also be used if desired.

Fig. 5 shows the embodiment of Fig. 1 wherein a photodiode (PD) is used to provide an in-situ measure of output light dosage. The output of the photodiode is coupled to a  
15 controller 40 having an associated control bus 40a. The control bus 40a, in this example, is coupled to the pump 20, to reactant source pumps 16c and 16d, and to a heater controller 18a (shown schematically as a switch). Based on the light intensity detected by the photodiode in the  
20 target area, the controller is enabled to selectively control one or more reactant parameters (e.g., temperature, concentration, flow rate, etc.) so as to provide a desired amount of light energy to the target area. Other optical detectors, such as photoresistors, can be used in place of  
25 the photodiode.

While the invention has been particularly shown and described with respect to preferred embodiments thereof, it will be understood by those skilled in the art that changes in form and details may be made therein without departing  
30 from the scope and spirit of the invention.

CLAIMS

What is claimed is:

1. An optical source for exciting a photosensitive drug that responds to light within a predetermined band of wavelengths, comprising a chemiluminescent source in combination with at least one fluorescer selected to output light within the predetermined band of wavelengths.

2. An optical source as in claim 1, wherein the chemiluminescent source is flowed during use.

3. An optical source as in claim 1, and further comprising means for heating said chemiluminescent source.

4. An optical source as in claim 1, and further comprising an active feedback system for controlling said output light.

5. An optical source as in claim 1, wherein said chemiluminescent source in combination with said at least one fluorescer are flowed through a conduit.

6. An optical source as in claim 1, wherein said chemiluminescent source in combination with said at least one fluorescer is provided within a fluid-containing patch.

7. An optical source as in claim 1, wherein said chemiluminescent source, in combination with said at least one fluorescer, is provided as a plurality of reactants, and further comprising:

a reservoir wherein said reactants are mixed; and

a pump for pumping the mixed reactants through a

conduit to a tissue to be treated.

8. An optical source as in claim 1, wherein said chemiluminescent source, in combination with said at least one fluorescer, is provided as a plurality of reactants, and further comprising:

a patch comprising a plurality of compartments, individual ones of said compartments containing one of said reactants; wherein

a mechanical deformation of said patch causes said compartments to rupture such that said reactants are released and mixed together.

9. An optical source as in claim 1, wherein said chemiluminescent source is comprised of an oxalate ester/hydrogen peroxide ( $H_2O_2$ ) system.

10. An optical source as in claim 1, wherein said chemiluminescent source is comprised of luciferase.

11. An optical source as in claim 1, wherein said at least one selected fluorescer is comprised of a rhodamine derivative.

12. An optical source as in claim 1, and further comprising a second fluorescer selected for shifting emission wavelengths of said at least one flourescer.

13. A catheter for insertion into a body cavity, said catheter having at least one region that is transparent to light having wavelengths within a predetermined band of wavelengths selected for exciting a photosensitive drug, said catheter comprising a conduit for flowing a chemiluminescent source in combination with at least one

fluorescer selected to output light within the predetermined band of wavelengths.

14. A patch for application to a surface of a tissue, said patch having at least one region that is transparent to light having wavelengths within a predetermined band of wavelengths selected for exciting a photosensitive drug, said patch comprising an internal chamber region for flowing therethrough a chemiluminescent source in combination with at least one fluorescer selected to output light within the predetermined band of wavelengths.

15. A patch for application to a surface of a tissue, said patch having at least one region that is transparent to light having wavelengths within a predetermined band of wavelengths selected for exciting a photosensitive drug, said patch having at least one region that is transparent to light having wavelengths within a predetermined band of wavelengths selected for exciting a photosensitive drug, said patch comprising a plurality of compartments, individual ones of said compartments containing one of a plurality of reactants; wherein a mechanical deformation of said patch causes said compartments to rupture such that said reactants are released and mixed together for forming a chemiluminescent source in combination with at least one fluorescer selected to output light within the predetermined band of wavelengths.

16. A method for generating light having wavelengths within a predetermined band of wavelengths selected for exciting a photosensitive drug, comprising steps of:

mixing a plurality of reactants for forming a chemiluminescent source in combination with at least one fluorescer selected to output light within the predetermined band of wavelengths;

exciting the at least one selected fluorescer by energy transfer from an energetic immediate in a chemiluminescent reaction to provide a fluorescent emission in the predetermined band of wavelengths; and

optically coupling the fluorescent emission to a tissue to be treated by the photosensitive drug.

17. A method as in claim 16, wherein the step of mixing includes a step of mixing the reactants in a reservoir, and wherein the step of optically coupling includes a step of causing a flow of the chemiluminescent source in combination with the at least one fluorescer to the tissue to be treated.

18. A method as in claim 16, wherein the step of mixing includes a step of combining the reactants within a patch that is to be applied to a surface of a tissue to be treated.

19. A method as in claim 18, wherein the step of combining includes an initial step of rupturing a plurality of reactant containing compartments within the patch.

20. A source of light having wavelengths within a predetermined band of wavelengths selected for exciting a photosensitive drug, comprising:

means for mixing a plurality of reactants for forming a chemiluminescent source in combination with at least one fluorescer selected to output light within the predetermined band of wavelengths, said mixing means causing an excitation of the at least one selected fluorescer by energy transfer from an energetic immediate in a chemiluminescent reaction to provide a fluorescent emission in the predetermined band of

wavelengths; and

means for optically coupling the fluorescent emission to a tissue to be treated by the photosensitive drug.

21. A source as in claim 20, wherein said mixing means is comprised of:

a reservoir coupled to a plurality of reactant sources;

means for introducing reactants from said plurality of reactant sources into said reservoir; and

means for causing a flow of mixed reactants out of said reservoir.

22. A source as in claim 20, wherein said means for optically coupling is comprised of a catheter having a transparent region.

23. A source as in claim 20, wherein said means for optically coupling is comprised of a patch having a transparent region.

24. A source as in claim 23, wherein said mixing occurs within said patch.

25. A source as in claim 20, and further comprising means for maintaining said chemiluminescent source at a predetermined temperature.

26. A source as in claim 20, and further comprising an active feedback system for controlling an intensity of said fluorescent emission.

1/2

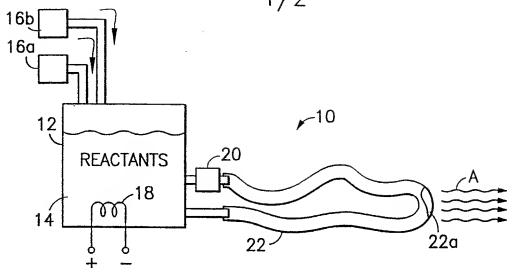


FIG. 1

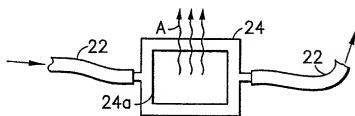


FIG. 2

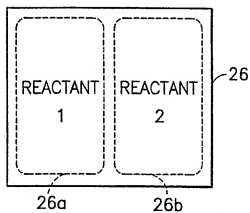


FIG. 3A

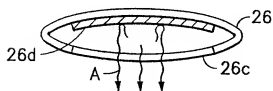


FIG. 3B

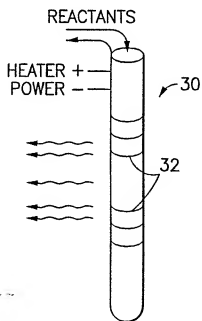


FIG. 4



2/2

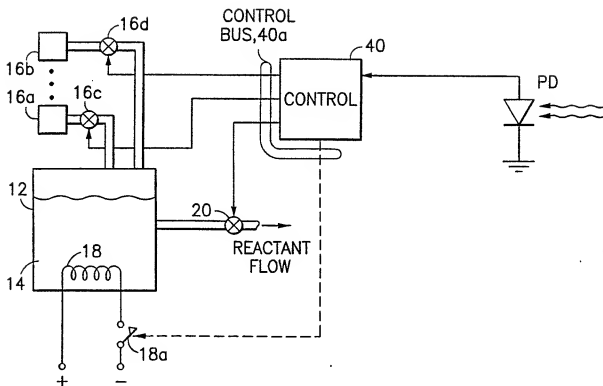


FIG.5

## INTERNATIONAL SEARCH REPORT

 International application No.  
 PCT/US98/01200

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61B 5/00, 06

US CL : 128/654, 665; 606/2, 3, 9; 607/88, 89

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/654, 665; 606/2, 2, 9; 607/88, 89; 606/2, 3, 9

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,889,129 A (DOUGHERTY et al.) 26 December 1989, entire document.	1, 2, 4, 5, 12 ----- 6, 9-11, 13, 14
Y	US 5,092,841 A (SPEARS) 03 March 1992, Abstract, and claim 1.	3
X	US 4,917,084 A (SINOFSKY) 17 April 1990, Abstract.	1
X	US 4,930,504 A (DIAMANTOPOULOS et al.), 05 June 1990, Abstract.	1
X	US 5,111,821 A (POTTER) 12 May 1992, Abstract.	1

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	*A* document member of the same patent family

Date of the actual completion of the international search

30 APRIL 1998

Date of mailing of the international search report

22 JUN 1998

 Name and mailing address of the ISA/US  
 Commissioner of Patents and Trademarks  
 Box PCT

Authorized officer

DAVID J. CHO

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/01200

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,527,350 A (GROVE et al.) 18 June 1996, Abstract.	1-26
X	US 5,572,996 A (DOIRON et al.) 12 November 1996, Abstract.	1